REMARKS

Claim 20 remains in the application. Claim 20 is the only claim in independent form.

Claim Rejection- 35-USC § 103

Claim 20 stands rejected under 35 U.S.C. §103(b) as being unpatentable over Sioud, *et al.* in view of WO 99/39210 to Miller, *et al.* The Office Action holds that Sioud, *et al.* teaches the analysis of the humoral response in patients with cancer; but does not specifically teach a "microarray of markers within sera". The Office Action further holds that Miller, *et al.* teaches a high-density protein array for proteome analysis and that it would have been *prima facie* obvious to one skilled in the art to have utilized the techniques of Sioud, *et al.* to biopan and select clones to array in a large format as presented by Miller, *et al.*

The present invention is a system for the identification of antigens to be included as markers in arrays for the immunological diagnosis of early stage cancer. It encompasses three features in a combination not found in the cited art, a combination which possesses improved properties not expected by Sioud, et al., or by the combination of Sioud, *et al.* and Miller, *et al.*

First, the invention uses the native humoral immune response to cancer, in all its natural diversity, as the source of antibodies with which to identify antigenic markers for inclusion in a diagnostic antigen array.

Second, the invention permits the user to identify not only antigenic markers expressed by tumor cells but also those relevant to normal and aberrant regulation of the anti-tumor response. As is well known in the art, the native humoral response to cancer includes not only antibodies to antigens encoded by

mutated or overexpressed oncogenes, but also regulatory antibodies, such as antibodies to CD44 and antiidiotypic antibodies. Furthermore, autoantibodies potentially useful in diagnosis, are provoked by various cancer pathologies. The capability to identify regulatory antigens associated with antibody response arises from the provision of random peptide libraries to screen the humoral response (page 17, lines 16-26), in addition to libraries derived from tumor cDNA. Claim 20 has been amended to encompass provision of both random and tumor cDNA phage display libraries.

Third, the antigen array identified by the invention is large and diverse enough to be used for microarray analysis (e.g. page 25, lines 23-31). This enables the user to diagnose cancer not only by the presence or absence of individual antibodies, but also by differences in the *patterns* of antibody response characteristic of tumor hosts and normal donors. This added higher level of analysis, the comparison of patterns, is made possible by the pattern recognition capabilities of microarray analysis well known in the art, and discussed by the applicant (page 57 line 5 to page 58 line 3).

The method disclosed by Sioud, *et al.* does use the native humoral response to cancer as the source of antibodies for screening antigens for diagnostic. It does not, however, permit the identification of antigens other than those expressed by tumor cells, such as regulatory antigens, for it discloses only tumor cDNA expression libraries as candidate antigens. Additionally, as recognized by the Office Action, Sioud, *et al.* do not teach a "microarray" of markers.

Applicant asserts that it would not have been obvious to one ordinarily skilled in the art to combine Sioud, *et al.* with the high density protein array of Miller, *et al.* The invention of Miller, *et al.* does utilize microarray analysis, but it does not teach the use of the entire diversity of the native humoral immune response to cancer to identify antigens to be included in an antigen array for the

diagnosis of cancer. The antibodies are provided as a secondary array which is used to interrogate a primary array of antigens which emulate the antigenic diversity of a cell, tissue, etc. The source of antibodies in this secondary array is not, and indeed cannot be, a native humoral response to cancer or any other disease. To be used as an array, the antibodies must be monoclonal antibodies or derivatives thereof, presented individually, one antibody to each potential antigen. To interrogate an unknown primary proteome panel of Miller, *et al.* with the unknown serum mixture of antibodies of Sioud *et al.* would not produce a useful result. There would be no way to specifically identify or characterize either an individual antigen or an individual antibody. Interrogating the phage display library of Sioud *et al.* with the secondary monoclonal antibody array of Miller *et al.* would identify a panel of monoclonal antibodies which react to tumor antigens, but those antibodies would have no relation to the native humoral response to cancer. The antigens thus identified would be useless as markers to detect host antibody profiles characteristic of cancer. Therefore even if there were a suggestion to combine the teachings of Sioud, *et al.* with those of Miller, *et al.*, the present invention provides improved results unexpected by the combination.

Claim 20 also stands rejected under 35 U.S.C. §103(b) as being unpatentable over Sioud, et al. in view of U.S. Patent Application Publication No. 2003/0003516 to Robinson, *et al.* The Office Action holds that Sioud, et al. does not specifically teach a "microarray" of markers within sera. The Office Action further holds that Miller, *et al.* teaches a high-density protein array for proteome analysis and that it would have been *prima facie* obvious to one skilled in the art to have utilized the techniques of Sioud, *et al.* to biopan and select clones to array in a large format as presented by Robinson, *et al.*

"[It is an] error to find obviousness where references 'diverge from and teach away from the invention at hand'". *In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988) (citing *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983)).

Robinson, *et al.* do disclose the use of a microarray of antigens and does interrogate them with the diverse products of a native humoral response to disease, in this case autoimmune disease or allergy. However, Robinson *et al.* teach away from combination their invention with that of Sioud *et al.* to arrive at a system for identifying antigenic markers for inclusion in a diagnostic antigen array. The invention of Robinson, *et al.* is not a marker discovery system but one intended to improve the use of known or suspected antigens in the process of diagnosis and treatment design. It is designed to address the "unmet need for methods of accurately and quickly performing diagnosis of the autoantigen repertoire being recognized by immune cells in clinical disease states, and for the translation of this knowledge into specific therapeutic modalities." (page 1 at 0008). All disclosed techniques and examples involve arrays of pre-identified antigens already suspected of causing disease. No claim specifies the identification of antigens for inclusion in a diagnostic array. The use of an array of unknown antigens is mentioned as an incidental speculative remark: "An autoantigen array...may include antigens optimized for a particular disease, while in another instance may include a library of unknown antigens to identify targets of the antibody response..." (page 6 at 0047), but there is no suggestion of how unknown antigens could be incorporated into the assay system in any useful way. Also lacking is any suggestion of identifying regulatory antigens associated with aberrant regulation of immune response. As stated in the Office Action "...Robinson teaches the use of arrays of epitopes ..to *screen* for disease..".

The remaining dependent claims not discussed above are ultimately dependent upon at least one of the independent claims discussed above. No prior art reference makes up for the deficiencies of that reference as applied against the independent claims as no prior art reference discloses or suggests the invention as set forth in the claims as discussed in detail above.

In conclusion, it is respectfully requested that the present amendment be entered in order to place the application in condition for allowance or at least in better condition for appeal. The application is placed in condition for allowance as it addresses and resolves each and every issue that remains pending. The claims have also been amended to clearly distinguish them over the prior art. The application is made at least in better condition for appeal as the amendment removes any issues thereby simplifying the issues on appeal. That is, each and every rejection has been overcome. Hence, it is respectfully requested that the amendment be entered.

If any remaining issues exist, Applicants respectfully request to be contacted by telephone at (248) 539-5050.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Terry Horst